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Neonatal bisphenol A exposure alters the prostate epigenome and increases cancer risk

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Susceptibility to prostate carcinogenesis was evaluated as a function of neonatal exposure to estradiol or low-dose Bisphenol A (BPA). Newborn rats were given high dose estradiol (E2, 25 μ g), low-dose estradiol (E2, 0.001 μ g), low-dose BPA (0.1 μ g) or oil on Days 1-5. At Day 90, rats were given empty tubes or T+E capsules for 16 weeks to drive hormonal carcinogenesis. At 7 months, prostates were examined for PIN lesions. Rats given high-dose E2 neonatally with or without adult T+E had a high PIN incidence and score. While rats given low-dose E2 exhibited a mild increase in PIN, the neonatal treatment did not influence PIN lesions induced by adult T+E treatment. Neonatal BPA alone did not induce prostate pathology. However, rats neonatally exposed to BPA followed by T+E in adulthood showed a significantly higher PIN incidence and score compared to control rats and the lesions were indistinguishable from neonatal high-dose E2 prostates. These findings indicate that environmentally relevant doses of BPA during early development increase prostate susceptibility to hormonal carcinogenesis. To determine the molecular underpinning of this developmental reprogramming, prostates from all treatment groups were screened for DNA methylation changes. Over 30 gene candidates were identified as differentially methylated following neonatal exposures. Several genes involved in intracellular signalling were evaluated in detail and shown to carry specific and persistent methylation alterations that resulted in aberrant gene expression with aging. We propose that neonatal estrogen reprogramming of adult prostatic disease susceptibility may be mediated through epigenomic alterations which promote prostate disease in the aging male.